Transcriptome sequencing of tumor subpopulations reveals a spectrum of therapeutic options for squamous cell lung cancer.

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Public Summary:
Our study is relevant to SCC in particular for it presents numerous potential options to standard therapy that target the entire tumor. In so doing, it demonstrates how transcriptome sequencing provides insights into the molecular underpinnings of cancer propagating cells that, importantly, can be leveraged to identify new potential therapeutic options for cancers beyond what is possible with DNA sequencing.

Scientific Abstract:
BACKGROUND: The only therapeutic options that exist for squamous cell lung carcinoma (SCC) are standard radiation and cytotoxic chemotherapy. Cancer stem cells (CSCs) are hypothesized to account for therapeutic resistance, suggesting that CSCs must be specifically targeted. Here, we analyze the transcriptome of CSC and non-CSC subpopulations by RNA-seq to identify new potential therapeutic strategies for SCC. METHODS: We sorted a SCC into CD133- and CD133+ subpopulations and then examined both by copy number analysis (CNA) and whole genome and transcriptome sequencing. We analyzed The Cancer Genome Atlas (TCGA) transcriptome data of 221 SCCs to determine the generality of our observations. RESULTS: Both subpopulations highly expressed numerous mRNA isoforms whose protein products are active drug targets for other cancers; 31 (25%) correspond to 18 genes under active investigation as mAb targets and an additional 4 (3%) are of therapeutic interest. Moreover, we found evidence that both subpopulations were proliferatively driven by very high levels of c-Myc and the TRAIL long isoform (TRAILL) and that normal apoptotic responses to high expression of these genes was prevented through high levels of Mcl-1L and Bcl-xL and c-FlipL-isoforms for which drugs are now in clinical development. SCC RNA-seq data (n = 221) from TCGA supported our findings. Our analysis is inconsistent with the CSC concept that most cells in a cancer have lost their proliferative potential. Furthermore, our study suggests how to target both the CSC and non-CSC subpopulations with one treatment strategy. CONCLUSIONS: Our study is relevant to SCC in particular for it presents numerous potential options to standard therapy that target the entire tumor. In so doing, it demonstrates how transcriptome sequencing provides insights into the molecular underpinnings of cancer propagating cells that, importantly, can be leveraged to identify new potential therapeutic options for cancers beyond what is possible with DNA sequencing.